REMARKS/ARGUMENTS

Reconsideration of this application and entry of this amendment are solicited. Claims 16, 19, 38, 39, 41 and 48-66 will be pending in the application upon entry of this amendment.

Discussion of Amendments to the Claims

No claims are deleted; four claims are amended. Independent claims 48 and 49 are amended to specify the therapeutic plasma concentration is maintained for a duration of at least 6 hours. Dependent claims 51 and 52, have been revised to depend from claims 48 and 49 and specify that T_{maint} is from 6 to 12 hours. Basis for the values of 6 and 12 hours is at page 18, line 7 of the description.

Salient Points of the Present Invention

The present invention sets out to provide nasal buprenorphine compositions for systemic action with:

a) relatively high maximum plasma concentrations

b) at a relatively short time after administration, **and**

c) which are relatively well sustained,

resulting in the major advantage when used in the treatment of pain of

i) relatively rapid onset of analgesia after administration,

ii) a closer to optimum level of analgesia **and**

iii) analgesia that is well sustained.

One of the ways in which this profile is achieved is to provide a liquid which is sufficiently fluid to be readily sprayed into the nose, but is sufficiently viscous and/or gels on the mucosa to hold the drug *in situ*.

Response to Prior Art-Based Rejections

discussed in the order presented in the Action:

Claims 48 to 52

Claims 48 and 49 relate to a buprenorphine composition and method of treatment defined by the plasma concentration-time profile obtained on administration. Both independent claims require that within 0.5 to 20 minutes a therapeutic plasma concentration of 0.4 to 5 ng/ml is reached which is maintained, as specified in this amendment, for at least 6 hours.

Such requirements are not fulfilled by the compositions of Eriksen. It is clear from Table 3 of Eriksen that although an initial concentration of 0.4 ng/ml is reached, by 6 hr it has decayed to 0.23 ng/ml. In contrast the present buprenorphine formulations maintain a level of 0.4 to 5 ng/ml or more at 6 hr and is not anticipated by Eriksen.

Although no §103 rejection of claims 48 to 50 has been made, it is commented on here for completeness. Eriksen fails to disclose the present buprenorphine formulations, since its resultant plasma level fall to 0.23 ng/ml in 6 hr. Eriksen is thus not a document that would be considered by one skilled in the art seeking to provide a buprenorphine composition which provides)relatively rapid onset of analgesia after administration,

ii) a close to optimum level of analgesia **and**

iii) analgesia that is well sustained.

Even if Eriksen were considered, it nowhere teaches to adjust its formulations to achieve the major advantages of

a) relatively high maximum plasma concentrations

b) at a relatively short time after administration, **and**

c) which are relatively well sustained at a level of 0.4 to 5 ng/ml or more at 6 hr.

The subject matter of these claims in their form as above amended is thus not only novel over the formulations of Eriksen, but Eriksen does not render these claims obvious.

Claims 1 -15, 38, 39, 41

A §103 rejection of claims 1 - 15, etc has been made over Eriksen as the primary citation viso Watts, Reich and Nairn. Its formulations differ from the present buprenorphine - pectin formulation as follows:

i) the presence of dextrose and the absence of pectin with a DE of less than 50% (at 5- 40 mg),

ii) a pH of about 7, and not 3 - 4.2,

iii) no teaching of the absence of divalent cations, and

iv) no teaching that the formulations of the citation gel on the nasal mucosa.

To recap, the present invention sets out to provide nasal buprenorphine compositions for systemic action which produce

a) relatively high maximum plasma concentrations

b) at a relatively short time after administration, **and**

c) which are relatively well sustained,

resulting in the major advantage when used in the treatment of pain of

i) relatively rapid onset of analgesia after administration,

ii) a closer to optimum level of analgesia **and**

iii) analgesia that is well sustained.

For the reasons set out for claims 48 to 50 above, in addition to not teaching physical features i) - iv), Eriksen fails to teach formulations that have the combination of a) and b) with c). It teaches a) and b), but not c). It is thus not a document that would be considered by one skilled in the art seeking to provide a buprenorphine composition which provides this combination of a), b) and c).

Even if Eriksen were used, it is not enough for Watts just to teach to adjust to achieve c) - maintenance of therapeutic plasma concentration levels, but that in doing so, the resultant formulation will have or retain a) and b) - relatively high maximum plasma concentrations at a relatively short time after nasal administration.

In the context of point 4. of *Graham v. John Deere*, the teaching of Watts must be read **as a whole** as it would be considered by one skilled in the art, and not with hindsight selectivity. It is agreed that Watts teaches to provide a nasal buprenorphine composition with a systemic activity profile of 'long retention in the nasal cavity', as cited in section 28 of the action.

It must however also be taken into consideration - as a whole - that Watts also clearly teaches the following:

Watts teaches that its formulations may be used for local and systemic administration. If for local administration, Watts teaches that the formulation **should not** enhance transmucosal absorption of a drug into systemic circulation, i.e. it **should not** give rise to any significant plasma concentration, still less at a short time after administration (p. 3, ll. 21 on). This is an essential part of the activity profile of the formulations of Eriksen, and Watts teaches directly away from it.

If for systemic administration, Watts teaches that its compositions are used to control the plasma concentrations of drugs, in particular to retard the transmucosal absorption of drugs which are readily absorbed, and where peak plasma concentrations are to be avoided (p.14, ll. 12 on). This is an essential part of the activity profile of the formulations of Eriksen, and Watts teaches directly away from it. Again, the thrust of the examples of Watts relate entirely to formulations which **do not** enhance transmucosal absorption of a drug.

In all aspects it teaches directly away from rapid high initial plasma levels, i.e. directly away from the formulations of Eriksen. Thus, even if Eriksen were used as a basis, Watts teaches that its formulations will desirably impair the rapid high plasma levels of Eriksen. Watts is thus not a document that would be combined with Eriksen by one skilled in the art in the reasonable expectation of providing formulations with

a) relatively high maximum plasma concentrations

b) at a relatively short time after administration, **and**

c) which are relatively well sustained.

The combination of Eriksen viso Watts thus cannot render these claims obvious.

The §103 rejection of claims 2 - 15, 38, 39, 41 has been made over Eriksen as the primary citation viso Reich and Nairn. These rejections stand or fall with claim 1, so no further comment is made here.

Claims 16 and 53 - 59

A §103 rejection of claims 16 and 53 to 59, etc has been made over Eriksen as the primary citation viso Koochaki.

Eriksen's formulations differ from the present buprenorphine - formulation as follows:

a) the presence of dextrose and the absence of chitosan and hydroxypropylmethylcellulose,

b) a pH of about 7, and not 3 - 4.8.

Koochaki's formulations differ from the present buprenorphine formulation as follows:

i) they are solid powder formulations, and not aqueous solutions, and

ii) to achieve this solid powder form, they have to contain very high percentages by weight of chitosan and hydroxypropylmethylcellulose, typically of the order of 87% (see its examples),

iii) they contain no buprenorphine as such.

The levels of chitosan and hydroxpropylmethyl cellulose in the present liquid formulations with the desired activity profile are 0.0002 to 0.035% (0.2 to 35 mg/ml = mg/g of aqueous solution). In contrast, Koochaki's formulations contain percentages by weight of chitosan and hydroxypropylmethylcellulose that are some 2,500 to 450,000 times greater than in the present compositions.

The very low percentages by weight of chitosan and hydroxypropylmethylcellulose in the present liquid formulations (0.0002 to 0.035% (0.2 to 35 mg/ml = mg/g of aqueous solution)) are **essential** to the activity profile of the present liquid and/or gel formulations, the desired activity profile being:

a) high maximum drug plasma concentrations,

b) at a relatively short time after administration, **and**

c) for the maximum plasma concentration to be well sustained.

For the reasons set out for claims 48 to 50 above, Eriksen is not a document that would be considered by one skilled in the art seeking to provide a buprenorphine composition which provides the combination of

a) relatively high maximum plasma concentrations

b) at a relatively short time after administration, **and**

c) which are relatively well sustained,

Even if Eriksen were used, it is not enough for Watts just to teach to adjust to achieve c) - maintenance of therapeutic plasma concentration levels, but that in doing so, the resultant formulation will have or retain a) and b) - relatively high maximum plasma concentrations at a relatively short time after nasal administration.

Koochaki nowhere teaches to adjust the formulations of Eriksen in the expectation of providing a nasal buprenorphine composition with the desired activity profile. The thrust of Koochaki is towards the solving the problem that it perceives with jelly and spray formulations for delivering drugs in the nasal cavity, viz the lack of sustained presence of the drug on the nasal mucosa (as symptomised by 'roll-back'), and the consequent lack of sustained release.

Furthermore, from the passage at page 3, lines 35 – 52, it can be seen that Koochaki is mainly concerned with delivering drugs in the nasal cavity which are for the local/topical treatment of nasal diseases, where it is necessary for such local/topical treatment to have a sustained presence of the drug on the nasal mucosa. Prolonged retention *in situ* merely potentially enhances sustained local levels of the medicament. It has absolutely nothing to do *per se* with enhancing rapid uptake and high initial systemic levels. Koochaki thus nowhere teaches anything about formulations which promote the transmucosal absorption of buprenorphine to give rapid high levels of the drug **systemically.**

The examiner is incorrect in his assertion (item 33) that Koochaki teaches to incorporate chitosan and hydroxypropylmethylcellulose into liquid buprenorphine compositions to arrive at the present liquid formulations. For the latter to be sprayable, these must form only 0.0002 to 0.035% (0.2 to 35 mg/ml = mg/g) of the aqueous solution.

Koochaki teaches that the only solution to the problem of ensuring a sustained presence of the drug on the nasal mucosa for the local/topical treatment of nasal diseases is to avoid any liquid and/or gel compositions and methods of treatment entirely, and to use such heavy loadings of chitosan and hydroxypropylmethyl-cellulose (that are some 2,500 to 450,000 times greater than in the present compositions) that they produce solid powder formulations. Such formulations are not said to be sprayable, and indeed Koochaki is entirely silent as to their mode of application. That is, Koochaki provides no incentive towards the present liquid formulations with the desired activity profile.

The combination of Eriksen viso Koochaki thus cannot render claim 16 obvious.

Claims 19, 60 - 66

The §103 rejection of claim 19 has been made over Eriksen as the primary citation viso Williams. Its formulations differ from the present buprenorphine - pectin formulation as follows:

i) the presence of dextrose and the absence of chitosan and a polyox, and

ii) a pH of about 7, and not 3 - 4.8.

For the reasons set out for claims 48 to 50 above, Eriksen is not a document that would be considered by one skilled in the art seeking to provide a buprenorphine composition for **systemic** action with

a) relatively high maximum plasma concentrations

b) at a relatively short time after administration, **and**

c) which are relatively well sustained,

resulting in the major advantage when used in the treatment of pain of

i) relatively rapid onset of analgesia after administration,

ii) a closer to optimum level of analgesia **and**

iii) analgesia that is well sustained.

Even if Eriksen were used as a basis for this quest, Williams nowhere teaches to adjust the formulations of Eriksen in the expectation of providing a nasal buprenorphine composition with the desired activity profile **systemically**.

Again, Williams must be read as a whole, and not have passages selected out of it with hindsight. There is no unambiguous teaching in Williams of specific formulations which comprise the combination of a chitosan and a polyox, or of a chitosan - polyox composition with the desired activity profile. Claim 6 and the thrust of the passages cited by the Examiner are to mucoadhesives that **are** polyox block copolymers; there is no clear teaching of a mucoadhesive that is a combination of chitosan and a polyox. If Williams teaches the skilled person anything, it is to incorporate polyox alone into the formulations of Erikson, not the specific combination of chitosan and polyox.

Even if that were not the case, the thrust of Williams is entirely towards formulations for delivering drugs to mucosa (e.g. nasal mucosa) for long-lasting local anaesthesia. Prolonged retention *in situ* merely potentially enhances sustained local levels of the medicament. It has absolutely nothing to do *per se* with enhancing rapid uptake and high initial systemic levels.

Moreover, Williams teaches local anaesthesia, *i.e.* a lack of or at most negligible transmucosal absorption of anaesthetic and consequently no or a negligible systemic plasma concentration.

Williams clearly teaches directly away from formulations with

a) relatively high maximum systemic plasma concentrations,

b) at a relatively short time after administration, and

c) sustained plasma levels.

Thus, even if Eriksen were used as a basis for his quest, Williams is not a document that would be considered by one skilled in the art seeking to adjust the formulations of Eriksen. The combination of Eriksen viso Williams thus cannot render claim 19 obvious.

Response to Double Patenting Concerns

In items 41-56 the examiner has made provisional double patenting rejections of various claims in sections over the copending '315 application. Applicants will leave a response to these provisional rejections in abeyance until the scope of the relevant '315 claims are clearer.

The examiner has also made a **non-provisional** obviousness double patenting rejections of various claims in sections 57 - 61 of the action over US 6 387 917 (Illum). This rejection is traversed. The thrust of Illum is entirely to compositions for parenteral or non-parenteral administration of a systemically acting opioid analgesic in which the solubilizing methanesulphonate anion enhances absorption of a drug. In particular, its examples are entirely towards the use of that salt of morphine.

There is no teaching whatsoever in Illum of formulations for the nasal cavity that comprise buprenorphine or a salt thereof. The gap between Illum and the present invention that must be filled in order to render the present invention obvious is a teaching in Illum or another document to select buprenorphine from the general opioids and to provide nasal compositions of it or its salts. There is no such teaching in Illum.

There must also be an incentive to make that change in the reasonable expectation of success of providing a formulation which will give

i) a relatively high maximum plasma concentration at a relatively short time after administration, **as well as**

ii) relatively well sustained plasma levels.

There is no such incentive.

Illum is thus not a document that would be considered by one skilled in the art seeking to provide a buprenorphine composition which provides the major advantage of

i) relatively rapid onset of analgesia after administration,

ii) a close to optimum level of analgesia and

iii) analgesia that is well sustained,

in the reasonable expectation of success. Illum thus does not render the relevant present claims obvious.

Summary

It is submitted that the application is in order for allowance. Entry of this amendment and avorable reconsideration of the application are requested.

Respectfully submitted,

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